

**REMARKS**

Claims 1-4, 8-37, and 46-48 are under examination. The claims have been amended to more particularly specify the claimed subject matter. No new matter has been added. Reconsideration is requested.

**Rejections Under 35 USC §102**

Claims 1-4, 8-10, 12-17, 19-21, 25-37 and 46-48 have been rejected as being anticipated by Bab et al (WO 95/00166). This rejection is traversed for the following reasons.

It is the Examiner's position that Bab et al (WO 95/00166) teach administering YGFGG in phosphate buffered saline (PBS) to mice once a day for twelve days, on day 8, mice were treated with a single X-ray radiation and on day 14, mice were sacrificed and their bone marrow was isolated and analyzed. The Examiner states that administration of this peptide stimulated the production of bone marrow cells.

The Examiner further indicates that while Bab et al (WO 95/00166) do not teach all the effects recited in claims 1, 8, 13, 15, 19, 25, 26, 28, 29, 30, 37, 46, and 48, they do perform the same administration of this peptide as in the present invention. The Examiner concludes that because the method steps in the instant application are the same, Bab et al (WO 95/00166) inherently teach the same effects as those recited in claims 1, 8, 13, 15, 19, 25, 28, 29, 30, 37, 46 and 48.

As will be described in detail below, the methods of the invention are based on the use of a known product, the YGFGG peptide (the OGP pentapeptide), which was shown as

exhibiting particular novel properties, specifically: 1) enhancement of multilineage stem cell mobilization to peripheral blood, 2) specific growth enhancing effect on certain lineage of circulating early stem cells (CD34<sup>+</sup>), and 3) specificity for myeloid cells, as exhibited by specific enhancement of growth of the pluripotent progenitors CFU-GEMM, CFU-Meg and CFU-Eo. These properties were hitherto unknown, and as will be described below, cannot be predicted from the Bab et al. citation (WO 9500166A), which discloses no enablement for such novel applications for the YGFGG pentapeptide.

As acknowledged by the Examiner, the only two Examples of the cited Bab et al. (WO 9500166A) reference demonstrate stimulatory effect of the OGP peptide (YGFGG) on the number of total bone marrow cells of irradiated and bone marrow transplanted mice.

The Examiner alleges that administration of this peptide as performed by Bab et al., although not teaching all the effects recited in claims 1, 8, 13, 15, 19, 25, 26, 28, 29, 30, 37, 46, and 48, inherently anticipates these claims.

Applicants disagree. It is respectfully submitted that Bab et al., provide sufficient enablement only for the treatment of irradiated and transplanted subjects, but that the effect on different hematological disorders and subjects undergoing chemotherapy would require undue experimentation, given the teachings of Bab et al., and therefore cannot be considered as enabling the different novel parameters defined by the claims.

Moreover, the present invention relates to the OGP(10-14) pentapeptide that enhances the mobility of multilineage stem cells and therefore increases the circulating stem cells. It is worthwhile emphasizing at this point that Bab et al., provide enablement only for enhancement of bone marrow cells, but makes no mention about cells in peripheral blood. It

is respectfully submitted that Bab et al is not enabling regarding peripheral blood cells, and is therefore not a valid reference in support of the rejection.

More particularly, the OGP(10-14) pentapeptide was clearly shown in the present application as exhibiting a specific growth-enhancing effect on a certain lineage of circulating early stem cells (CD34<sup>+</sup>). It should be stressed that CD34 antigen is present only in approximately 2-3% of the human bone marrow cells, specifically in early myeloid cells that express the CD33 antigen but lack the CD14 and CD15 antigens, and in early erythroid cells that express the CD71 antigen and dimly express the CD45 antigen, and in all hematopoietic colony-forming cells in bone marrow and blood, including unipotent (CFU-GM, BFU-E) and pluripotent progenitors (CFU-GEMM, CFU-Mix, and CFU-Blast). Normal peripheral blood lymphocytes, monocytes, granulocytes, and platelets do not express the CD34 antigen. Therefore, the fact that the pentapeptide OGP(10-14) used in the methods of the invention enhances the mobility of early stem cells and moreover specifically increases growth of a particular precursor cell type that constitutes only very small portion of the bone marrow population, is surprising, novel and inventive, and cannot be regarded as inherently taught by the disclosure of Bab et al.

Moreover, the fact that the OGP(10-14) pentapeptide is specific for myeloid cells, was particularly advantageous for the treatment of myeloidic disorders, as demonstrated by Example 4, which shows the effect of this OGP(10-14) pentapeptide on rescuing the cellularity in samples taken from patients suffering from Idiopathic myelofibrosis. Therefore, if at all, this reference enables only the use of this known pentapeptide for hematopoietic reconstruction after bone marrow transplantation of irradiated subjects (mice), but not, as

alleged by the Examiner, for the treatment of hematological disorders. In this regard, it should be stressed that in view of the particular importance of stimulation of specific subset of cells, the Examiner's rejection of claims 2, 3, 12, 14, 27, 31-36 and 47, as only describing an inherent effect is not appropriate, and therefore should be withdrawn.

The present invention further shows that OGP(10-14) pentapeptide specifically enhances the growth of the pluripotent progenitors CFU-GEMM [these progenitors may differentiate into BFU-E (which differentiate into Red blood cells), CFU-Meg (as shown in the Figure attached hereto as **Exhibit A**, these progenitors can differentiate into the megakaryocytes and macrophages) and to CFU-Eo (that can differentiate into eosinophils and basophils).

Moreover, the further progenitor cell assay shown in Example 3 of the present application (page 45), indicates that this OGP(10-14) pentapeptide increases the BFU-E unipotent cells that differentiate into erythrocytes, but not CFU-GM (that differentiate into neutrophils and monocytes which are the precursors of macrophages). It should be noted that BFU-E are progenitor circulating cells while macrophages are not circulating cells. The demonstrated effect of OGP on a particular subset of cells has different applications which could not be inherently taught by the non-enabling disclosure of Bab et al., (WO 9500166A), which does not suggest such indications, and even were they suggested, would require undue experimentation to achieve them. Moreover, it should be appreciated that the effect of a known hematopoietic growth factor cannot be predicted based only on its ability to stimulate bone marrow cells. An illustrative example of this is provided by the present application. The differential effect of OGP(10-14) was compared to the well known hematopoietic growth

factor G-CSF that was shown to be specific for CFU-GM (but not for CFU-GEMM and BFU-E). As shown in Example 3, OGP (10-14, YGFGG) exhibited a significant effect on CFU-GEMM and BFU-E but not CFU-GM. In view of the prior art, the Bab reference does not provide sufficient enablement such that the skilled person would have anticipated such selective effect and its consequent applications.

Thus, as surprisingly shown by the present invention, the OGP(10-14) peptapeptide demonstrates specific growth effect on a particular pluripotent myeloid (and not lymphoid) early CD34<sup>+</sup> stem cells, and more particularly, on circulating stem cells, the BFU-E. These particular properties of the peptide firstly disclosed by the invention enable the use of this peptide in methods of treatment of particular hematological disorders and particularly of myeloid disorders.

These particular effects of OGP(10-14) on a certain cell lineage, together with its effect on bone marrow samples of IMF patients, are novel, surprising and cannot be considered as inherently taught by the non-enabling disclosure of Bab et al.

Moreover, the OGP(10-14) peptide used by the composition of the invention enhances mobilization of hematopoietic stem cells, and particularly of CD34<sup>+</sup> cells.

Release of hematopoietic stem cells into the peripheral blood of patients in response to chemotherapy or cytokine stimulation was first documented in the late 1970s and early 1980s, as indicated by To et al., [attached hereto as **Exhibit B**]. This process, termed mobilization, mimics the enhancement of physiological release of progenitors from the bone marrow reservoir in response to stress signals during injury and inflammation, and has been shown to be induced clinically or experimentally in animal models by a wide number of

molecules: cytokines, such as G-CSF (granulocyte colony-stimulating factor), granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin (IL)-7, IL-12, stem cell factor (SCF), and flt-3 ligand; chemokines like IL-8, Mip-1 $\alpha$ , GRO $\beta$ , or SDF-1, and the chemotherapeutic agents cyclophosphamide (Cy) and paclitaxel. These molecules differ in their time frames for achieving mobilization, the types of cells mobilized, and efficiency. G-CSF is the most commonly used agent, usually administered daily at a dose of 5-10  $\mu$ g/kg for 5-10 days, sometimes in combination with cyclophosphamide. It should be noted that some patients, and also a minority of healthy individuals, are poor mobilizers, as indicated by Fu et al. [attached hereto as **Exhibit C**], as will be discussed hereafter.

Regulation of hematopoietic stem cell release, migration, and homing to the bone marrow, as well as the mechanism of different mobilization pathways, involve a complex interplay between adhesion molecules, chemokines, cytokines, proteolytic enzymes, stromal cells and hematopoietic cells, however the mechanism is not fully understood [Lapidot and Petit, attached hereto as **Exhibit D**]. Moreover, human stem cell mobilization and positive selection of immature CD34<sup>+</sup> cells have become the preferred source of repopulating stem cells for clinical transplantation. Potential advantages of peripheral blood progenitor cell transplantation include the avoidance of marrow harvest and anesthesia and the ability to expand the pool of eligible patients to include those with marrow involvement with tumor or prior pelvic radiation therapy, which frequently precludes marrow harvest. Another advantage of using peripheral blood progenitor cells compared to marrow has been enhanced engraftment of myeloid cells and platelets, resulting in significantly decreased medical

support such as blood product use, antibiotic use and length of hospitalization [Fu et al., **Exhibit C**].

Currently, mobilized progenitors are the preferred and major source of stem cells harvested for autologous [attached hereto as **Exhibit E**], allogeneic [attached hereto as **Exhibit F**] and even from related donors with one fully mismatched HLA haplotype [attached hereto as **Exhibit G**] transplantations, due to the higher stem cell yield, leading to faster engraftment, and decreased procedural risks compared to harvested bone marrow cells.

Surprisingly, the present application clearly demonstrates (in Example 3, particularly as indicated on page 45, first paragraph) the similar effect of OGP(10-14) peptide and G-CSF on **mobilization** of stem cells to the **peripheral blood**. These experiments were performed on mice that were **chemoablated** by treatment with CFA (cyclophosphamide) and injected daily with OGP(10-14) or with G-CSF. Blood samples were collected from the tested animals and analyzed for different WBC counts. Moreover, these blood samples were also analyzed for the existence of CD34<sup>+</sup> cells. The results obtained clearly indicate significant increase in peripheral blood cellularity, and particularly of CD34<sup>+</sup> cells, which according to Keating et al. [attached hereto as **Exhibit I**], should be regarded as surrogate marker for **mobilizing capacity**.

Moreover, the results shown in Figures 2 and 3 of the present application clearly indicate that OGP (10-14) increases mobilization, and particularly of CD34<sup>+</sup> stem cells. These findings indicate that the OGP(10-14) pentapeptides used by the methods of the invention may be used as a **mobilizing agent**, comparable to the well established G-CSF, and not only as an agent having stimulatory effect on bone marrow cells of irradiated and transplanted

subject, as demonstrated by Bab et al. Such indication could not be predicted by the skilled artisan, in view of the teaching of the prior art.

It must be stressed that the fact that prior art citation WO 9500166A, teaches the enhancement activity of OGP and peptides derived therefrom on bone marrow stem cells after irradiation and bone marrow transplantation, has no relationship to the surprising findings described in the present application. The present application demonstrates the mobilization activity of these peptides, and not just their beneficial effect on reconstruction of hematopoietic microenvironment after transplantation and irradiation, as taught by Bab et al. This mobilization effect shown by the invention demonstrates the feasibility of efficient preparation of transplant (effective collection from donors due to increased mobilization to peripheral blood, as recited in claim 28). Therefore, it is particularly submitted that the Examiner's rejection of claim 28 is incorrect.

The demonstrated specific effect of this pentapeptide on particular cell subsets, establishes uses thereof for treatment of hematological disorders. From the teachings of Bab et al., it was not obvious to the skilled artisan, to predict that OGP peptides may induce mobilization of stem cells to the peripheral blood. Moreover, as stated in the USPTO MPEP, *"The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. In re Rijckaert, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art); In re Oelrich, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). "To establish inherency, the extrinsic evidence 'must make clear that the*

*missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient."* (emphasis added). Thus, since Bab et al., only examined bone marrow cells, but did not examine any blood samples of the treated animals, it cannot provide any enablement for examination of the mobilization effect demonstrated by the present application.

Still further, it is known in this field that the proliferative activity of a given compound on bone marrow stem cells does not necessarily mean that such compound can induce mobilization, and the ability of the same compound to induce mobilization cannot be predicted without undue experimentation. For example, IL-3 has a proliferative effect on primitive hematopoietic cells *in vitro* and gives rise to a moderate increase in leukocyte and platelet counts upon *in vivo* administration, nonetheless has little activity in mobilization. The increased stromal cell proliferation seen in patients receiving IL-3 may result in enhanced retention of hematopoietic progenitor cells and may therefore explain the relatively poor efficacy of such protocols [To et al., **Exhibit B**]. Moreover, the skilled practitioner cannot predict that a compound which is known to have an inhibitory activity on proliferation of stem cells, would not exhibit enhancement of mobilization. For example, MIP-1 $\alpha$  (Macrophage inflammatory protein-1 $\alpha$ ) inhibits primitive stem cell proliferation and has been investigated as a myeloprotective agent during chemotherapy. Murine studies with BB10010, genetically engineered variant of human MIP-1 $\alpha$  showed that a single subcutaneous injection caused a twofold increase in circulating CFU-S and cells with marrow repopulating ability

(MRA). Although G-CSF increased the circulating levels of CFU-S and MRA 20- to 30-fold, a single injection of BB10010 after 2 days of G-CSF increased the levels 30- and 100-fold, respectively [To et al., **Exhibit B**].

Still further, the mobilization process, which is a multi-step process, is not an obvious procedure and therefore cannot be predicted by the skilled artisan, from the proliferation enhancing effect of OGP on bone marrow cell population following transplantation, demonstrated by Bab et al. (WO 9500166A). For example, a substantial number of patients, especially after extensive chemotherapy which leads to BM aplasia, older patients and also a minority of healthy individuals, are poor mobilizers [Fu et al., **Exhibit C**]. Factors such as increasing age and longer intensive chemotherapy treatment in old multiple myeloma patients, inversely correlate with successful mobilization. These patients are usually treated with higher doses of G-CSF, GM-CSF followed by G-CSF, or a combination of G-CSF and SCF. It was further reported that collection of an adequate graft was achieved only in 27% of the tested CML patients treated with high doses of Imatinib [attached hereto as **Exhibit H**]. Decreased ability to mobilize stem cells was also reported in AML patients [**Exhibit I**]. These studies stress the need to identify and characterize further agents, such as the peptides of the invention and develop better strategies appropriate for poor mobilizers.

Applicant therefore submits that the mobilization properties of the OGP peptides, which were shown for the first time in the present application, provide a particular novel property for the pentapeptide used by the methods of the invention that could not be predicted by the disclosure of Bab et al, which examined only the effect of bone marrow cells obtained from femoral bone of irradiated and transplanted mice and therefore render the present set of

claims novel and inventive over the prior art. As stated in the MPEP, "[a]n invitation to investigate is not an inherent disclosure" where a prior art reference "discloses no more than a broad genus of potential applications of its discoveries." *Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1367, 71 USPQ2d 1081, 1091 (Fed. Cir. 2004) (explaining that "[a] prior art reference that discloses a genus still does not inherently disclose all species within that broad category" but must be examined to see if a disclosure of the claimed species has been made or whether the prior art reference merely invites further experimentation to find the species." (emphasis added). Therefore, it is respectfully submitted that the Examiner's rejection of claims 20 and 21, asserting that the hematological disorders are anticipated by the irradiated and transplanted mice of Bab et al., is incorrect, since, if anything, Bab et al (WO 9500166A) indicates that the peptides of the invention may be considered as general and non-specific growth factors, and therefore teaches away from the findings presented in the present application.

These particular effects of OGP(10-14) on a certain cell lineage, together with its effect on bone marrow samples of IMF patients, are novel, surprising and could not be predicted by the prior art. Therefore, the subject matter of the present set of claims should not be considered as inherently anticipated by Bab et al.

Additionally, the Examiner alleged that claims 19, 25, 26 and 29 require "exposing" cells to YGF<sub>GG</sub>, which is anticipated by the administration to mice taught by Bab et al. The Examiner particularly indicates that the term "exposing" does not particularly limit the manner in which the cells and the peptide interact. The Examiner further explains that the term "exposing" does not require, for example, that the cells be cultured *in vitro* and

contacted directly with YGFGG peptide. Claim 25 has been amended to be restricted to "*in vitro*" exposure of cells, and claim 29 was canceled. It is respectfully submitted that the restriction of claims 19 and 26 to "*in vitro*", is not necessary in view of the arguments detailed above. Reconsideration and withdrawal of this portion of the rejection are respectfully requested.

The Examiner further asserted that claims 9 and 30 require that the subject be undergoing irradiation, and in day 8 of the method of Bab et al., mice were irradiated and injected with the peptide. Claims 9 and 30 have been amended to be limited to subjects receiving chemotherapy. Reconsideration and withdrawal of this portion of the rejection are respectfully requested.

For all of the above reasons, it is respectfully submitted that claims 1-4, 8-10, 12-17, 19-21, 25-37 and 46-48 are not anticipated by Bab et al. Reconsideration and withdrawal of the rejection are respectfully requested.

Claims 1-4, 8, 10, 12-17, 19-21, 25-37, and 46-48 have been rejected under 35 USC § 102(b) as being anticipated by Chen et al. (2000, Journal of Peptide Research 56: 147-156). This rejection is traversed for the following reasons.

Applicants respectfully submit that the Chen et al reference assesses the role of individual amino acid residues in the YGFGG peptide on mitogenic activity, which showed a very high correlation between osteoblastic and fibroblastic cell cultures. Although at page 155 first column, administration of this peptide in PBS to mice is described, it must be emphasized that these mice underwent bilateral ovariectomy. After subcutaneous injections of OGP peptide, mice were killed and examined for trabecular bone density and trabecular

thickness (as described by the second column of page 155). These ovariectomized mice were used only as an *in vivo* model for assessing the osteogenic effect of the peptide. This reference is silent with regard to irradiation, chemotherapy or transplantation. The *in vitro* experiments included exposure of osteoblastic MC<sub>3</sub>T<sub>3</sub> E<sub>1</sub> and fibroblastic NIH 3T3 cells to the OGP pentapeptide. Nothing in the experiments described by this publication teach or even hint the particular effect of OGP on a specific subset of hematopoietic stem cells that are particularly relevant for the treatment of hematological, and preferably, myeloproliferative disorders. The arguments against the "inherent disclosure" in view of Bab et al WO 9500166A rejection, disclosed in section I above, also apply to this ground of rejection, since also Chen et al. provide no enablement for the new properties and applications demonstrated by the invention. Therefore, Chen et al does not anticipate the present invention. Reconsideration and withdrawal of the rejection are respectfully requested.

Claims 1-4, 8-10, 12-17, 19-21, 25-37 and 46-48 have been rejected under 35 USC § 102(b) as being anticipated by Gurevitch et al. (1996, Blood 88: 4719-4724) taken in the light of Bab et al. (1999, Journal of Peptide Research 54; 408-414). The Examiner specifically refers to the term "having" in these claims, contending that because the specification does not explicitly teach that "having" means "consisting of" this term has been interpreted as "comprising". The term "having" was amended to "consisting of" in these claims to further clarify the invention. Furthermore, it is noted that as detailed above regarding the Bab et al document, there is no disclosure or suggestion in Gurevitch et al. of the novel properties of the compounds that allow use for enhancing the mobilization of multilineage hematopoietic

stem cells to peripheral blood as is presently claimed. Like Bab et al., Gurevitch et al. does not teach or suggest the use of the compounds for this method. Reconsideration and withdrawal of the rejection are respectfully requested.

### **Rejections Under 35 USC §103**

Claims 8, 11, 15, 18, 20 and 22-24 were rejected under 35 USC § 103(a) as being unpatentable over Bab et al. taken with Takayama et al (1999, U.S. Patent 5, 910, 303). This rejection is traversed for the following reasons.

The claims were interpreted by the Examiner as being drawn to various methods comprising administration of a peptide of SEQ ID NO. 1 to a subject or exposing cells to said peptide. The Examiner indicated that Bab et al. do not teach treatment of myeloproliferative disorders or specifically increase of circulating CD34+ stem cells or CFUs in subject with myeloproliferative disorder, but that Takayama et al. teach treating myeloproliferative disorders, including myelofibrosis, with an agent that promote platelet and leukocyte production and reversing the damage to bone marrow caused by irradiation therapy. According to the Examiner, a skilled artisan would have the reasonable expectation of success in treating myeloproliferative disorders including MF, with the pentapeptide of Bab et al., which teaches that this peptide stimulates bone marrow cell production and subsequent repopulation of immune system.

It is respectfully submitted that for the reasons outlined above, Bab et al. fails to disclose the novel properties that allow the use of the oligopeptides of the invention for enhancing the mobilization of multilineage hematopoietic stem cells to peripheral blood as is

presently claimed. The secondary reference, Takayama et al, fails to remedy this omission. Accordingly, it is respectfully submitted that Bab et al and Takayama et al, taken together, do not render the claims obvious. For this reason, reconsideration and withdrawal of the rejection are respectfully requested.

Claims 8, 11, 15, 18, 20 and 22-24 have been rejected under 35 USC § 103(a) as being unpatentable over Gurevitch et al taken with Bab et al. and Takayama et al. This rejection is traversed for the following reasons.

It is the Examiner's view that Gurevitch teach that OGP stimulates bone marrow cell production and subsequent repopulation of the immune system (Table 3 and Figure 1). The Examiner therefore concludes that the skilled artisan would have been motivated to modify the invention for the expected benefit of treating myelofibrosis in a patient, and therefore, the invention is obvious in view of these three citations.

First, it is respectfully submitted that Gurevitch et al and Bab et al. fail to anticipate the invention as broadly claimed for the reasons presented above. The secondary reference, Takayama et al, fails to remedy this omission. For this reason, it is submitted that this combination of references does not render the subject claims obvious. Reconsideration and withdrawal of the rejection are respectfully requested.

Furthermore, Applicant respectfully submits that Takayama et al relates to the use of IFN $\gamma$  in combination with a "biologically active substance" that may be selected from IL-3, IL-6, G-CSF, GM-CSF, SCF, TPO, EPO and M-CSF, for the treatment of thrombocytopenia and leucopenia induced by a variety of diseases and by radio and chemo treatment. This patent demonstrates that IFN $\gamma$  in itself induces the reduction of the platelet level in mice, but

strongly augments the activity of promoting the platelet production of biologically active substance such as IL-3 (see column 7, last paragraph). In fact, all eight figures of this patent describe the effect of combination of IFN $\gamma$  and IL-3 on thrombocytopenia and leucopenia. The Examples referred to by the Examiner are only illustrative and indicate the preparation of an agent comprising IFN $\gamma$  and IL-3 (Example 1, column 12) and IFN $\gamma$  and GM-CSF (Example 2, column 12), for the treatment of a variety of diseases including myelofibrosis. Therefore, if anything at all, this patent teaches the combination of IFN $\gamma$  with another known "substance" and particularly, IL-3, for treatment of thrombocytopenia and leucopenia. Reading this citation in view of Bab et al and Gurevitch et al, by the "skilled" artisan, as suggested by the Examiner, would result in the combination of IFN $\gamma$  with OGP pentapeptide. This however was not disclosed and claimed by the present invention. Moreover, as indicated in our arguments detailed in point (I) above, different known growth factors, including the factors listed in the "substance" list of Takayama et al., exhibits different "mobilization" properties. It is interesting to note, that particularly IL-3, which is the preferred factor in Takayama et al., has for example very poor activity in mobilization [according to To et al., **Exhibit B**]. Therefore, this patent by itself or in combination with any of the references cited by the Examiner, if at all, teaches away from the invention and illustrates the need of examining each and every known or novel factor for different activities such as mobilization or particular enhancement of specific cell lineage. As such, Takayama demonstrates the need of undue experimentation in view of the prior art. Thus, all three references are not relevant for the inventive step of the present invention.

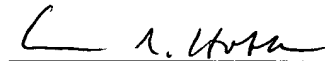
**Non-Statutory Obviousness-type Double patenting**

The Examiner has rejected claims 1-4, 8, 12,-15, 19, 25-29, 31-36 and 46-48 on the ground of non-statutory obviousness-type double patenting over claim 20 of U.S. Patent No. 5, 814, 610 ("610 patent"), which shares six of the inventors with the instant application. The Examiner points to the phrase "a subject in need thereof" in the claims, indicating that claim 20 of the '610 patent refers to a method of treatment of various osteological conditions in "human" by administering the peptide of SEQ ID NO. 1. The Examiner has taken the position that all humans and animals fall within the scope of "subject in need thereof", and concludes that the scope of claim 20 of the '610 patent is completely encompassed by the scope of the cited instant claims. The claims in the present application have been restricted to a subject receiving irradiation or chemotherapy or suffering from hematological disorder, and are submitted to be free of this rejection. Reconsideration and withdrawal of the rejection are respectfully requested.

All rejections having been addressed, it is respectfully submitted that this application is in condition for allowance, and Notice to that effect is respectfully requested.

Respectfully submitted,

Date: 2/28/07



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